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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,481	12/22/1998	NICHOLAS VAN BRUGGEN	11669.41US01	2987

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/218,481	Applicant(s) VAN BRUGGEN ET AL.	
	Examiner Jennifer E Hunt	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,3-6,8-21 and 27-29 is/are pending in the application.

4a) Of the above claim(s) 3-6,11-21 and 27-29 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 and 8-10 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The examiner assigned to this application has changed. Please address future correspondence to Jennifer Hunt, Art Unit 1642.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office actions.

Claims 1 3-6, 8-21, and 27-29 are pending in the application. Claims 3-6, 11-21, and 27-29 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1 and 8-10 are considered herein.

Claim Rejections Withdrawn

The rejections of claim 8 under 35 USC 112 first paragraph for failing to provide an enabling disclosure for the full scope of the invention, and for introducing new matter are withdrawn in light of the amendments thereto.

The rejections of claim 8 under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in light of the amendments thereto.

The rejection of claims 1, and 8-10 under 35 USC 102(b) as being anticipated by WO 94/10202, as evidenced by Taber's Cyclopedic Medical Dictionary , 1989, 16th Edition, FA Davis Company, Philadelphia, p 742, and Risau, Acta Neurochirurgica

Supplementum, 1994, 60:109-112 is withdrawn in light of the new grounds of rejection set forth below.

New Grounds of Rejection

Claims 1 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing vasogenic cerebral edema which is caused by increased expression of VEGF, by administering a VEGF antagonist comprising an anti-hVEGF antibody, does not reasonably provide enablement for reducing of any other type of cerebral edema, including cytotoxic cerebral edema by administering a VEGF antagonist comprising an anti-hVEGF antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The specification discloses a method of reducing cerebral edema in rats by pre-administering a flt-IgG antagonist prior to occlusion of the cerebral artery. The rats

which were pre-administered a flt-IgG antagonist experienced reduced levels of cerebral edema compared to the control group.

The claims are broadly drawn to a method of reducing any type of cerebral edema by administering any hVEGF antagonist comprising an anti-hVEGF antibody.

The art teaches that there are two general types of cerebral edema. Vasogenic edema is caused by vascular leakage, and is often characterized by breakdown of the BBB and over expression of VEGF. Cytotoxic edema is caused by cellular swelling, and does not involve VEGF over expression. See Kempski, Seminars in Nephrology 21(3), pages 303-307, May 2001, or Schilling et al., Adv. Experimental Med Biol, Vol. 474, pages 123-141, 1999, (especially page 124, section 1). Thus the art teaches that there are types of cerebral edema which are not caused by or characterized by over expression of VEGF.

Thus treatment of cerebral edema with a VEFG antagonist comprising an anti-hVEGF antibody would not be expected by one of skill in the art to reduce cerebral edema, in types of cerebral edema which are not caused or mediated by hVEGF over expression, and therefore inhibition of VEGF would not alleviate the symptoms.

Thus there is no guidance or objective evidence that the instant method would be effective for reducing non-VEGF induced cerebral edema. The instant method specifically antagonizes the VEGF edema pathway, and a VEGF antagonist would not be expected to be an effective treatment in a non-VEGF pathway.

Therefore one of skill in the art would not be enabled to practice the full scope of the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, and 8-10 are rejected under 35 U.S.C. 103(a) as being anticipated by WO 94/10202, Ferrara et al., published May 11, 1994.

As set forth in previous Office Actions, the claims are drawn to a method of treating a mammal having edema comprising administering to said mammal an effective amount of hVEGF antagonist wherein the antagonist comprises an anti-VEGF antibody. Dependent claims recite that the antibody consists of murine variable domains and human constant domains, that the antibody is humanized, and that the antibody is monoclonal.

WO 94/10202 discloses a method of treating a tumor comprising administering to the mammal a therapeutically effective amount of a hVEGF antagonist sufficient to reduce the size of the tumor and discloses that within the scope of the invention antagonists include monoclonal antibodies that bind to hVEGF (p. 4, lines 23-24) and variants of said monoclonal antibodies including chimeric and humanized variants, including antibodies consisting of murine variable domains and human constant

domains (p. 8, lines 13-27) and specifically states that the invention is useful for treating glioblastoma and edema associated with brain tumors (page 3, lines 1-2).

The only difference between the instant invention and WO 94/10202 is that WO 94/10202 fails to specifically exemplify the use of an anti-hVEGF antibody to treat cerebral edema. However, in view of the clear suggestion by WO 94/10202 to use the anti-hVEGF antibody to treat cerebral edema, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the hVEGF antibody antagonists of WO 94/10202 to treat cerebral edema.

Arguments:

Applicant argues that the state of the prior art was not clear that administration of a VEGF antagonist would result in the reduction of cerebral edema in a mammal. Specifically, applicant argues that the method of WO 94/10202 was directed to treating angiogenesis, and thus cannot anticipate methods of reducing cerebral edema. Applicant further argues that example 4 of WO 94/10202 fails to show a reduction of cerebral edema *in vivo*. Applicant's arguments filed 7/14/2001 have been fully considered but they are not persuasive.

With regard to the state of the prior art, as taught by Berkman et al., The Journal of Clinical Investigations, Vol. 91, pages 153-159, 1993, VEGF over expression has been correlated to cerebral edema. Berkman et al. teaches that increases levels of VEGF mRNA correlates with cerebral edema, and that VEGF may provide a target for treating cerebra edema associated with VEGF over expression. Kalkanis et al.,

Journal of Neurosurgery, Vol. 85, pages 1095-1101, 1996, teaches that VEGF production plays a significant role in edema formation. Further, with regard to treatments directed to angiogenesis, while it is true that the method of WO 94/10202 is directed to a method of inhibiting angiogenesis, the method of WO 94/10202 is also directed to a method of reducing cerebral edema (see page 2, line 29-page 3, line 4, and also page 16, lines 25-37). Applicant's arguments regarding example 4 are not persuasive, in light of the teachings above. While example 4 may not specifically teach reduction of cerebral edema in vivo, the teachings of reduction of cerebral edema are supported by other portions of the specification. Further, the teachings of example 4 are not relied on for the rejection, and were merely cited to exemplify the efficacy of hVEGF antibodies in general, in the inherent method of inhibition of VEGF activity in general (including angiogenesis *and* edema)

Claims 1, and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Criscuolo, Yale Journal of Biology and Medicine, Vol. 66, pp277-314, 1993, or Fischer et al., Molecular Brain Research, Vol. 60, pp 89-97, 1998, in view of WO 94/10202, Ferrara et al., published May 11, 1994.

As set forth in previous Office Actions, the claims are drawn to a method of treating a mammal having edema comprising administering to said mammal an effective amount of hVEGF antagonist wherein the antagonist comprises an anti-VEGF antibody. Dependent claims recite that the antibody consists of murine variable

domains and human constant domains, that the antibody is humanized, and that the antibody is monoclonal.

Crisculo et al. teaches a method of reducing cerebral edema in a mammal, comprising administering an hVEGF antagonist (dexamethasone) effective to reduce the volume of cerebral edema in the brain of the mammal (see pages 303-305).

Fischer et al. teaches a method of reducing cerebral edema in a mammal, comprising administering a hVEGF antagonist (dexamethasone, methohexital, or thiopental) effective to reduce the volume of cerebral edema in the brain of the mammal (see page 95-page 96).

Crisculo et al. and Fischer et al. fail to teach that the hVEGF antagonist comprises an anti-VEGF antibody, that the antibody consists of murine variable domains and human constant domains, that the antibody is humanized, and that the antibody is monoclonal.

WO 94/10202 teaches hVEGF antagonists including monoclonal antibodies that bind to hVEGF (p. 4, lines 23-24) and variants of said monoclonal antibodies including chimeric and humanized variants, including antibodies consisting of murine variable domains and human constant domains (p. 8, lines 13-27) and specifically teaches that the antagonists can be used to treat edema.

Therefore because WO 94/10202 teaches the use of antagonists including anti-hVEGF antibodies to treat edema associated with brain tumors and because Crisculo et al. and Fischer et al. teach the use of antagonists of hVEGF to treat cerebra edema, it would have been *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made to use the anti-hVEGF antibodies of WO 94/10202 to treat cerebral edema.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner
Art Unit 1642

jeh
November 19, 2001

SHEELA HUFF
PRIMARY EXAMINER